IB03/06072

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1292/Del/02*** *dated* ***20th December 2002.***

Witness my hand this 13th day of April 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

1292-DEL-02

20 DEC 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE FORMULATION OF TAMSULOSIN"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. GIRISH JAIN

b. SEETHARAMAN SRITHARAN

c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 2343126; 2342001 – 10; 8912501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, GIRISH JAIN, SEETHARAMAN SRITHARAN, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(GIRISH JAIN)

b.

(SEETHARAMAN SRITHARAN)

c.

(ASHOK RAMPAL)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685794** dated **15.11.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **20TH** day of **DECEMBER,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

ABSTRACT

The present invention relates to a process for preparing controlled release pharmaceutical compositions of tamsulosin as individual unit or multiple unit formulation comprising an enteric-coated spherical core obtained by adding release controlling agent to a mixture of tamsulosin and spheronizing agent.

1292-02

FORM 2

20 DEC 2002

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE FORMULATION OF TAMSULOSIN

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for preparing controlled release pharmaceutical compositions of tamsulosin or its pharmaceutically acceptable salts thereof. More particularly, the invention relates to a controlled release individual unit or multiple unit formulation comprising a spherical core obtained by adding release controlling agent to a mixture of tamsulosin and spheronizing agent.

Tamsulosin is 5–[(2R)–2–[[2–(2–ethoxy–phenoxy) ethyl] amino] propyl]-2-methoxy benzene sulfonamide. It is an α_1-adrenoceptor blocking agent, exhibiting selectivity for α_1-receptors in the human prostate. It is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

The pharmacokinetic studies of tamsulosin show that it is absorbed from the intestine and is almost completely bioavailable.

US Patent 4,772,475 discloses an oral pharmaceutical controlled release multiple unit formulation in which the individual units comprise a granulation product of a release controlling agent, physiologically active substance and units-forming substance (s). The patent emphasizes that the unit-forming substance (crystalline cellulose) should at least be 50% by weight. The drug containing units of this invention has a high mechanical strength and can control dissolution rate without enteric coating.

The object of the invention is to develop a composition, which releases the drug gradually in the intestine where it is completely absorbed.

We have now discovered that enteric-coated, controlled release formulation of tamsulosin provides release at the desired site. The formulation of the present invention can be prepared with less than 50% w/w of spheronizing agent.

The present invention thus relates to a process of preparing a controlled-release pharmaceutical composition of tamsulosin, wherein the composition comprises:

(a) a spheroid core comprising:
    (i) Tamsulosin,
    (ii) 10-45% w/w of spheronizing agent,
    (iii) rate-controlling polymer(s) and;
(b) an enteric coating over the spheroid core.

Another aspect of the present invention is to provide a process for preparing a controlled release pharmaceutical composition of tamsulosin, comprising: (a) granulating a mixture of tamsulosin, spheronizing agent and rate controlling agent(s), (b) extruding the granulated mixture to obtain extrudates; (c) spheronizing the extrudates to obtain spherical cores: (d) drying the spheroid cores; and (e) coating the spheroid cores with an enteric polymer.

Thereafter, the coated spheroid cores are filled into capsules or compressed into tablets in an amount effective to provide a therapeutic dosage of tamsulosin when ingested orally by a patient.

The term spheroid is conventional in the pharmaceutical art and means a spherical granule having a diameter of between 0.1mm and 2.5mm.

Tamsulosin according to this invention comprises free base, pharmaceutically acceptable salts or isomers of tamsulosin thereof. The pharmaceutically acceptable salts may include hydrochloride, hydriiodide, hydrobromide, hydrogen fumarate and the like. Tamsulosin constitutes about 0.03-0.33% w/w of the formulation.

The spheronizing agent, according to this invention may comprise any pharmaceutically acceptable material, which may be spheronized together with the active ingredient to form spheroid cores. The most commonly used spheronizing agent is microcrystalline cellulose. The microcrystalline cellulose employed may be, for example, Avicel PH 101 or Avicel PH 102 commercially available from FMC Corporation. The spheronizing agent may be present in an amount ranging from 10% to 45% w/w.

The rate controlling agent(s) according to the present invention may include enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes and mixtures thereof.

Suitable enteric polymers include those known in the art, such as hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, polymethylacrylates and copolymers of acrylic and methacrylic acid (commercially available under the trade name of Eudragits). Of particular, relevance to this invention is Eudragit L30D-55 (anionic aqueous polymer dispersion of methacrylic acid – ethyl acrylate copolymer), Eudragit L100-55 (Spray-dried Eudragit L30D-55 which can be reconstituted as aqueous dispersion), Eudragit L100 (anionic polymer powder solubilizing above pH 6.0) and Eudragit S100 (anionic polymer powder solubilizing above pH 7.0).

Suitable waxes may be selected from hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids such as stearic acid and oleic acid and mixtures thereof.

Suitable water-insoluble polymers include ethyl cellulose, cellulose acetate, copolymers of polyethylene and vinyl acetate, methacrylic acid methyl methacrylate copolymers with quaternary ammonium groups such as those sold under the trade name Eudragit RL, Eudragit RS and Eudragit NE, and the like.

Suitable examples of the alkaline metal salts of a higher fatty acid include magnesium stearate, zinc stearate, calcium stearate, and the like.

Suitable water-soluble polymers may include polyvinylpyrrolidone, carboxymethylcellulose sodium, hydroxyl propyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, methylcellulose, and mixtures thereof.

The rate-controlling agent(s) may comprise about 20-90% w/w of the formulation.

The rate controlling agent(s) in accordance with this invention may also act as binder and may be added as such or dissolved or dispersed in an appropriate solvent system and the resulting solution or dispersion is then used to granulate the active agent. The resulting granulated mass may then be subjected to extrusion and spheronization. This method of incorporation allows the rate-controlling agent(s) to more effectively retard drug release.

Optionally, in addition to the active ingredient, spheronizing agent and rate controlling agent(s), the spheroid cores may also contain other pharmaceutically acceptable excipients, which act in one or more capacities as plasticizer, diluents, colorants or flavoring agents.

Diluents of the present invention may be selected from any conventional diluents such as lactose, starch, sugar alcohols and sucrose.

The controlled release composition according to this invention may be prepared by:

a. granulating a mixture comprising tamsulosin, spheronizing agent and rate controlling agent(s) with water,
b. extrusion of the granulating mixture to give extrudates; and
c. spheronizing the extrudates until spherical cores are formed.

Alternatively, granulation according to step a) may be carried out with a dispersion of rate-controlling agent(s).

The pharmaceutical composition according to the present invention further includes an enteric coating over the spheroid core. This coating will substantially eliminate dissolution in the acidic environment of the stomach but will dissolve sufficiently to permit release in a controlled manner over an extended period in the intestine.

Examples of some enteric coatings are disclosed in US 5,225,202, which is incorporated by reference fully herein. US 5,225,202 discloses enteric-coated pharmaceutical composition utilizing neutralized hydroxypropyl methylcellulose phthalate (HPMCP) coating. As set forth in US 5,225,202 some examples of coating employed are beeswax and glyceryl monostearate, beeswax, shellac and cellulose, shellac and stearic acid; neutral copolymer of methacrylic acid and methacrylic acid methyl ester (Eudragits) or a neutral copolymer of polymethacrylic acid esters containing metallic stearates.

Although Eudragits are the preferred enteric coating materials, the invention is not limited in this respect and other enteric coating polymers known in the art may also be employed, for example, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate succinate and the like.

Most of the enteric coating materials are acidic in nature and hence may cause chemical instability when in contact with active ingredient. However, this can be avoided by using suitable alkalizing agents like sodium hydroxide, potassium hydroxide, calcium carbonate, sodium carboxymethylcellulose, magnesium oxide and magnesium hydroxide. The enteric coating also contains a plasticizer, which may be selected from triethyl citrate, triacetin, diethyl phthalate, dibutyl phthalate, polyethylene glycol, propylene glycol, glycerol, tributyl citrate, and the like. The enteric coating may also include anti-adherent or tack-modifiers as inert aid in the stability of coating process. Suitable tack-modifier may be selected from talc, kaolin or colloidal anhydrous silica. The coating may also include opacifier like titanium dioxide.

The enteric coating layer can be formed on the surface of the spheroid cores, using conventional coating methods, for example fluidized or pan coating.

Compositions according to the invention may finally be filled into capsules or sachets or compressed into tablets using conventional pharmaceutical techniques.

The following examples illustrate various aspects of the present invention. These examples are for illustration only and should not be construed as limiting the scope of the invention.

EXAMPLE 1

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	126
	Magnesium stearate	20
	Starch	64.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	79.0
	Purified water	q.s.
Enteric coat	Methacrylic acid ethyl acrylate copolymer	6.59
	Sodium hydroxide	0.08
	Triacetin	0.99
	Talc	1.31
	Titanium dioxide	0.11
	Purified water	q.s

EXAMPLE 2

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	126
	Glyceryl mono stearate	20
	Starch	64.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	79.0
	Purified water	qs
Enteric coat	Same as for example 1	

EXAMPLE 3

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	118
	Stearic acid	18
	Starch	60.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	74
	Povidone	5
	Purified water	qs
Enteric coat	Same as for Example 1	

Process:

1. Tamsulosin hydrochloride is dissolved in water and the solution is used to granulate microcrystalline cellulose, in a mixer.
2. Granulate of step 1 is dried in fluidized bed dryer at 60°C and sieved to a particle size of less than 600 μ.
3. Magnesium stearate/ glyceryl mono stearate/ stearic acid and starch are sieved to a particle size of less than 600 μ and mixed with granulate of step 2 in a mixer.
4. The blend of step 3 is granulated with the dispersion of methacrylic acid-ethyl acrylate copolymer (Eudragit L30D 55) in a rotary mixer grinder. Example 3, same blend is further granulated by 10% solution of povidone in water.
5. Granulate of Step 4 is extruded through a bore of inner diameter of 1mm.
6. The extrudates of step 5 are spheronized-using spheronizer fitted with plate of 3.25 mm pitch.
7. Spherical cores obtained in step 6 are dried in fluidized bed dryer at 60°C for one hour.
8. Enteric coating dispersion of Eudragit L100: 55 is prepared by dispersing enteric coating materials in water.
9. The spherical cores of step 7 are coated with the dispersion of step 8, to a weight gain of 3.33% w/w.
10. The coated cores of step 9 are filled in capsules.

The resulting capsules of Example 1 were compared with FLOMAX capsules (containing 0.4mg tamsulosin marketed by Boehringer Ingelheim) for in vitro release of tamsulosin. The dissolution studies were performed using USP Apparatus II at 50 rpm in 500ml phosphate buffer, pH 6.8. The results are shown in Table 1.

Table 1: Comparative in vitro release data of tamsulosin from capsules of Example 1 and FLOMAX capsules of Boehringer Ingelheim using USP dissolution apparatus II/ 500 ml/ pH 6.8, phosphate buffer/ 50 rpm

Time (hrs)	Cumulative Percent release of tamsulosin (%)	
	Capsules of Example 1	FLOMAX capsules
1	45	39
2	71	61
4	90	90
6	94	107

WE CLAIM:

1. A process for preparing a pharmaceutical composition for controlled release of tamsulosin, wherein the composition comprises:
   (a) a spheroid core comprising:
   (i) Tamsulosin,
   (ii) 10-45% w/w of spheronizing agent,
   (iii) rate-controlling polymer(s) and;
   (b) an enteric coating over the core.
2. The process according to claim 1 wherein the core is prepared by spheronization process.
3. The process according to claim 2 wherein the spheronization process comprises:
   a. granulating a mixture comprising tamsulosin, rate-controlling agent(s), spheronizing agent,
   b. extrusion of granulates to form extrudates using extruder.
   c. spheronizing the extrudates until spherical cores are formed.
4. The process according to claim 2 wherein the spheronization process comprises:
   a. granulating a mixture comprising tamsulosin and spheronizing agent with dispersion of rate-controlling agent(s),
   b. extrusion of granulates to form extrudates using extruder.
   c. spheronizing the extrudates until spherical cores are formed.
5. The process according to claim 1 wherein tamsulosin may include free base, pharmaceutically acceptable salts or isomers of tamsulosin thereof.
6. The process according to claim 5 wherein pharmaceutically acceptable salts of tamsulosin may include hydrochloride, hydriiodide, hydrobromide, hydrogen fumarate and the like.
7. The process according to claim 6 wherein the pharmaceutically acceptable salt of tamsulosin is hydrochloride.
8. The process according to claim 7 wherein tamsulosin hydrochloride is present in concentration of 0.03 – 0.33% w/w of the total composition.
9. The process according to claim 1 wherein the spheronizing agent is microcrystalline cellulose.
10. The process according to claim 1 wherein the rate-controlling agent(s) may include enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes and mixtures thereof.

11. The process according to claim 10 wherein the rate-controlling agent(s) is present from about 20-90% w/w of the total composition.

12. The process according to claim 10 wherein enteric polymer(s) may be selected from hydroxylpropyl methylcellulose phthalate, cellulose acetate phthalate, methacrylic acid and ethyl acrylate copolymer.

13. The process according to claim 12 wherein the enteric polymer is methacrylic acid and ethyl acrylate copolymer.

14. The process according to claim 10 wherein waxes may be selected from hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids and mixtures thereof.

15. The process according to claim 14 wherein the wax is glyceryl monostearate.

16. The process according to claim 14 wherein the wax is stearic acid.

17. The process according to claim 10 wherein water soluble polymers may be selected from polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropyl methylcellulose, hydroxyethylcellulose, methyl cellulose or mixtures thereof.

18. The process according to claim 10 wherein water insoluble polymers may be selected from ethyl cellulose, cellulose acetate, and methacrylic acid-acrylic acid copolymers with quaternary ammonium groups or mixtures thereof.

19. The process according to claim 10 wherein alkaline metal salts of higher fatty acid may be selected from magnesium stearate, zinc stearate, calcium stearate or mixtures thereof.

20. The process according to claim 19 wherein alkaline metal salt of higher fatty acid is magnesium stearate.

21. The process according to claim 1 wherein the spheroid core may also contain other pharmaceutically acceptable excipients

22. The process according to claim 21 wherein the pharmaceutically acceptable excipients may comprise plasticizers, diluents, colorants or flavoring agents.

23. The process according to claim 1 wherein the enteric coating is done with enteric polymers selected from hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid or mixtures thereof.

24. The process according to claim 23 wherein the enteric coating may additionally consist of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

25. The process according to claim 1 wherein the composition may be filled into capsules or sachets or compressed into tablets.

26. A process for preparing a pharmaceutical composition for controlled release of tamsulosin hydrochloride, comprising:

a. granulating a mixture of tamsulosin hydrochloride, starch and 42% w/w microcrystalline cellulose with methacrylic acid-ethyl acrylate copolymer;

b. extruding granulates to form extrudates;

c. spheronizing the extrudates; and

d. enteric coating the spheroids.

Dated this 20TH day of December, 2002.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary